COMPOUNDED TRANSDERMAL PAIN THERAPY – A DRUG OVERVIEW

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Objectives

- Compare the pros and cons of transdermal analgesia
- Explore the use of compounded agents:
  - Their mechanism of action
  - Evidence supporting their use
- Identify appropriate candidates for transferal pain therapy

Pathophysiology[1]

- **Nociceptive Pain**
  - Nociceptors (pain detecting nerves) send signals from the painful site to the spinal cord and brain for interpretation and reaction.
    1. *Somatic*
       - Arise from skin, bone, joint, muscle, or connective tissue
       - Easier to locate than visceral pain
       - More intense pain
    2. *Visceral*
       - Arise from internal organs
       - Dull pain
       - Harder to pinpoint

Pathophysiology[1]

- **Neuropathic Pain**
  - Result of nerve damage, abnormality of nerve pathway
  - Examples: Post-herpetic neuralgia, diabetic neuropathy
- **Functional Pain**
  - Abnormal operation of the nervous system
  - Examples: fibromyalgia, irritable bowel syndrome, tension-type headache, non-cardiac chest pain

Classifications of Pain[1,3]

1. **Acute pain**
   - Results from disease, inflammation, or tissue injury that comes suddenly
   - Subsides quickly
2. **Chronic pain**
   - Persist over long period of time
     - Weeks, months to years
   - Maybe resulted from changes of receptors and nerve fibers

Transdermal: Advantages[2]

- Can minimize systemic absorption
  - Less side effects
- Avoidance of first pass metabolism
- Ease of administration
  - Convenient and painless administration
  - Improve patient compliance
  - Oral dosing is not feasible for patient (unconscious or nauseated patients)
- Alternative formulation in special populations
  - Elderly
  - Pediatrics

Transdermal: Disadvantages[2]

- Topicals have appropriate molecular size and physiochemical properties in order to penetrate the skin
  - Size <500 Da
    - Example: Clonidine 230Da
- Aqueous and lipid solubility
- Skin permeability varies in different population
- Certain disease states alter penetration
  - Healthy vs. disease skin
- Localized skin irritation and erythema can occur (Contact Dermatitis)

Molecular Size[2]

DRUG	Dalton(Da)	DRUG	Dalton(Da)
Amitriptyline	277	Gabapentin	171
Baclofen	213	Ibuprofen	206
Benzocaine	165	Ketamine	237
Bupivacaine	288	Ketoprofen	254
Carbamazepine	236	Lidocaine	234
Clonidine	230	Naproxen	230
Cyclobenzaprine	275	Tetracaine	264
Diclofenac	296	Piroxicam	331

Why Compound?

- A natural fit to a complementary medical practice and the whole patient concept.
- The ability to customize therapy to fit the individual needs of a patient.
  - Instead of a one-size-fits-all approach of commercially available drugs, the possibilities with a compounded prescription are endless.

Pain Management

Chronic pain may have a myriad of causes and perpetuating factors, and therefore can be much more difficult to manage than acute pain, requiring a multidisciplinary approach and customized treatment protocols to meet the specific needs of each patient

- **Customize:**
  - NSAID Ketoprofen, Ibuprofen, Naproxen, Piroxicam, Diclofenac
  - Local Anesthetic Benzocaine, Bupivacaine, Lidocaine, Tetracaine
  - Muscle Relaxant/Anti- Spasmodic Baclofen, Cyclobenzaprine, Guaifenesin, Gabapentin, Clonidine
  - Tri-Cyclic Anti-Depressant Amitriptyline
  - NMDA-antagonist Ketamine, Magnesium
  - Mu Agonists Loperamide

Medications Used in Transdermal Delivery

Drug	Strength	Mechanism
Amitriptyline	2-5%	NE Reuptake inhibitor
Baclofen	1-20%	$GABA_{\beta}$ Agonist
Benzocaine	10-20%	Anesthetic
Bupivicaine	0.5-5%	Anesthetic
Clonidine	0.1-0.2%	Alpha-2 Agonist
Cyclobenzaprine	0.5-2%	Muscle Relaxant
Deoxy-D-Glucose-2	0.1-2%	Antiviral/Neuropathic Pain
Dexamethasone	0.2-2%	Anti-inflammatory
Dextromethorphan	5-10%	NMDA Receptor Antagonist

Medications Used in Transdermal Delivery

Drug	Strength	Mechanism
Diclofenac	2-30%	NSAID
Diphenhydramine	4-10%	Voltage Regulated Na^{+} & Ca^{++} Blockade
DMSO	5-10%	NSAID + Penetration Enhancer
Gabapentin	4-10%	Glutamate Antagonist
Guaifenesin	10%	Muscle Relaxant
Ibuprofen	2-10%	NSAID
Indomethacin	15-20%	NSAID
Ketamine	5-10%	NMDA Receptor Antagonist
Ketoprofen	10-30%	NSAID
Tetracaine	5-10%	Local Anesthetic

Medications Used in Transdermal Delivery

Drug	Strength	Mechanism
Lidocaine	2-10%	Anesthetic
Loperamide	5-10%	Mu agonist
Magnesium Chloride	2-25%	NMDA Antagonist
Mexelitine	2-10%	Na+ Channel Antagoniost
Naproxen	5-10%	NSAID
Nifedipine	1-16%	Non-NMDA Ca^{+2} Channel Antagonist
Pentoxifylline	5-10%	TNF_{α} Inhibitor, Peripheral Vasodilator
Piroxicam	0.5-30%	NSAID

NSAIDS

- Diclofenac
- Ibuprofen
- Ketoprofen
- Piroxicam
- Indomethecan
- Flurbiprofen

- Peripheral MOA:
  - COX Inhibitors
- Topical Effects:
  - Anti-inflammatory
  - Analgesic
- Works Great to treat:
  - Arthritis related inflammation
  - Muscle Pain
  - Nerve Pain

Ketoprofen Trial [12]

- **Comparison of Ketoprofen, Piroxicam, and diclofenac gels in treatment of Acute Soft-Tissue Injury in General Practice**
- open-label, comparative, parallel-group, randomized , multicenter, general practice study comparing the efficacy, tolerability and acceptability of treatment of Ketoprofen, piroxicam, and diclofenac gel
- 1575 patients with moderate to severe injury
- **Treatment arm:**
  - Ketoprofen gel 2.5% (1048)
  - Piroxicam gel 0.5% (263)
  - Diclofenac gel 1% (264)
- **Direction:**
  - Ketoprofen gel 2.5%, Apply 4-5 g three times daily with or without measuring device 5 days
  - Piroxicam gel 0.5% , Apply 1g three times daily 5 days
  - Diclofenac Gel 1%, Apply 2g to 4g three times daily for 5 days
    - Patient's were instructed to apply the gel by massaging it into the affected area, and to avoid covering the area with any occlusive dressing or protective bandage.
    - Treatment with paracetamol or coproxamol was permitted as rescue medication for symptomatic relief
- **Assessment**
  - Acceptability of treatment (4 point scale)
  - Global assessment of any change in the injury at the end of treatment and determine the usefulness of the measuring device
  - Physician evaluated the overall response to treatment using a four point scale
  - Observe adverse events were noted

Results:

- Physician Global assessment of treatment response showed that improvement in the effect of injury was better with Ketoprofen gel than with Piroxicam (74% vs. 65% p=0.0001), slightly better than with diclofenac (74% vs. 71).
- **Ketoprofen gel showed greater improvements in degree of stiffness (71% vs. 64% p=0.013), patient assessment of pain on pressure (81% vs. 78% p=0.02), and pain on movement (83% vs. 77% p=0.01) than piroxicam gel.**
- Global assessment of improvement of injury was significantly higher with Ketoprofen gel than with piroxicam gel (p=0.0002)
- Improvement of mobility was significantly higher with ketoprofen gel (without the measuring device, 34% vs. 22% p=0.006)
  - Measuring device appeared to offer little benefit
- **Incidence of drug-related events was very low: ketoprofen gel (0.7%), Diclofenac gel (1.1%), piroxicam gel (2.3%). Local skin reaction at the site of application was the common drug-related event. (erythema, rash, itching)**
- Ketoprofen gel was preferred by most patients because it was easier to rub than piroxicam gel (89% vs. 81%p=0.001), apply(p<0.002) with less staining (p=<0.001) and rated by more patients as having a cooling effect than either comparator (79% vs. 49% piroxicam vs. 60% diclofenac p=<0.001)

Local Anesthetics

Benzocaine

Bupivacaine

Lidocaine

Tetracaine

- Peripheral MOA:
  - Blockade of voltage gated Sodium Channels
- Topical Effects:
  - Analgesic
  - Minimizes nerve response
  - Numbing effects
- Works Great to treat:
  - Diabetic Neuropathy
  - Neuralgias
  - Complex Regional Pain Syndrome
  - Post Herpatic Neuralgia

Gabapentin

- Peripheral MOA:
  - Blocks voltage gated Calcium Channel Blocker
- Topical Effects:
  - Minimize Nerve Response
  - Reduce Neuropathic Sprouting
- Works Great to treat:
  - Allodynia / Hyperalgesia
  - Diabetic Neuropathy
  - Post Herpatic Neuralgia
  - Migraine
  - Complex Regional Pain Syndrome

Gabapentin Trial[10]

- **Topical Gabapentin in the treatment of localized and Generalized Vulvodynia**
- Studied the effects of 2%-6% Gabapentin in lipoderm base
- A retrospective study
- (50) Women diagnosed with generalized or localized vulvodynia from January 2001 to December 2006
  - Hormonal therapies and anticonvulsants were more common prior treatment for women with generalized vulvodynia while topical lidocaine in women with localized vulvodynia
  - **Treatment arm:**
    - (18) 2% Gabapentin 9=localized, 9=generalized
    - (10) 4% Gabapentin 7=localized 3=generalized
    - (22) 6% Gabapentin 16= localized, 6=generalized
- Direction: Apply 0.5 mL TID
  - Max daily dose: 30-90 mg for a minimum of 8 weeks duration of therapy

Gabapentin Trial[10]

- **RESULTS:**
  - Localized vulvodynia
    - Mean pain score was significantly reduced from 7.92 to 2.71(mean change -5.21, 95% CI -5.59 to -4.42, p<.001, 95% CI for % 6-37%)
  - Generalized vulvodynia
    - Mean pain score was reduced from 5.82 to 2.00 (mean change -3.82, 95% CI -5.25 to -2.38, p<.001, 95% CI for % 28-79%)
  - Use of topical Gabapentin for this disorder alleviate the pain, increase patient acceptability and tolerability, minimized ADR's and increase patient compliance.
  - **Common adverse effects of oral Gabapentin were not reported by any of the 50 patients studied in this trial**

Muscle Relaxants

Baclofen

Cyclobenzaprine

Guaifenesin

- Peripheral MOA:
  - Decreases excitatory neurotransmitter release
- Topical Effects:
  - Relieves muscle spasticity
- Works Great to Treat:
  - Deep Muscle Pain
  - Myofacial Pain

Tri-Cyclic Antidepressants

Amitriptyline

Desimipramine

Imipramine

Nortriptyline

- Peripheral MOA:
  - Activation of Adenosine receptors
  - Inhibits sodium, potassium and Calcium Channels
- Topical Effects:
  - Minimizes nerve respose
  - Provides Analgesia
- Works Great to treat:
  - Allodynia / Hyperalgesia
  - All types of Neuropathic Pain

NMDA Antagonists

Ketamine

Magnesium Chloride

- Peripheral MOA:
  - Inhibits NMDA excitatory pathways
- Topical Effects:
  - Minimizes Nerve Response
  - Analgesia
  - Numbing effects
- Works Great to treat:
  - All types of neuropathic pain
  - Pre-treat painful wounds / hyperalgesic areas

Baclofen, Amitriptyline, Ketamine[14]

- **A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCTG trial N06CA**
- **Purpose:** evaluate a topical Baclofen, AmitriptylineHCl, and Ketamine (BAK) gel to alleviate neuropathic pain, numbness, and/or tingling of chemotherapy-induced peripheral neuropathy (CIPN)
  - Secondary goals include the evaluation of function, general pain, and toxicity.
- **Treatment arm:**
  - Baclofen 10mg, 40mg Amitriptyline HCl, 20mg ketamine gel
  - placebo gel (PLO)
- **Direction:** Apply one level spoonful of gel topically to each area of pain, numbness, and or tingling, twice a day, in the morning and before bed for 4 weeks duration. (max of 4 spoonfuls of gel per application)
  - **Primary endpoint**: changes in the sensory neuropathy subscale measured by the European Organization for research and Treatment of Cancer (EORTC)→ 20 item questionaire→ assess sensory, motor and autonomic symptoms and functioning.
  - Participants completed this questionnaire at baseline, before starting the study and at 4 weeks
- 150 total patients→ 75 (BAK), 75 (placebo)

Baclofen, Amitriptyline, Ketamine[14]

- **BAK gel resulted more improvement in sensory neuropathy** (p=0.053); difference 95% CI 4.3(-0.6, 9.3)
  - Mean change from baseline SD of 8.1(15.05) in BAK arm
  - Mean change from baseline SD of 3.8 (15.52) in placebo arm
- **BAK gel resulted statistically improvement in motor neuropathy** (p=0.021); difference 95% CI 5.3(0.9, 9.7)
  - Mean change from baseline and SD were 7.1 (13.72) for BAK arm
  - Mean change from baseline and SD were 1.8 (14.05) for placebo arm

- **No significant differences in toxicities were observed between the BAK arm and the placebo through the 4 weeks of the study**
- Blood was drawn during the double-blind phase on a small subset of participants (N=8) to evaluate systemic absorption
  - 4 (BAK), 4(Placebo, no detectable levels)
  - For BAK group:
    - 2 undetectable levels of all 3 drugs
    - 1 barely detectable amitriptyline, no detectable ketamine and baclofen
    - 1 low therapeutic levels of baclofen but undetectable levels of amitriptyline and ketamine

Mu Agonists

Loperamide

Morphine

- Peripheral MOA:
  - Mu receptor (opioid) agonist
- Topical Effects:
  - Analgesia
- Works Great to treat
  - Arthritis
  - Hyperalgesia

LD Naltrexone for Fibromyalgia Trial

- **Low-Dose Naltrexone for the Treatment of Fibromyalgia**
- randomized, double-blind, placebo-controlled crossover study assessing the efficacy, and tolerability of low-dose naltrexone in the treatment of fibromyalgia
- 31 women with fibromyalgia
- **Treatment arm:**
  - Naltrexone 4.5 mg PO at bedtime (16)
  - Placebo (15)
- **Study duration:** 20 weeks
  - Placebo (4 weeks)→naltrexone (12 weeks) →follow-up (4 weeks)

    OR
  - Naltrexone (12 weeks)→placebo (4 weeks) →follow-up (4 weeks)
- **Direction:**
  - Naltrexone 4.5 mg PO at bedtime
- **Assessment:**
  - Reduction of baseline pain using scale 0-100
    - Pain measured in final 3 days in each condition
  - Satisfaction using single-item visual analog scale
  - Mood using single-item visual analog scale
  - Sleep quality using single-item visual analog scale

LD Naltrexone for Fibromyalgia Trial

- **Results**

Intervention	4.5 mg naltrexone	Placebo	p-value
Reduction in baseline pain	28.8%	18%	0.016
Increase in satisfaction	11.1%	3.2%	0.045
Mood improvement	10.7%	2.1%	0.039
Sleep quality improvement	10.4%	9.2%	0.575

- **Conclusion**
  - Low-dose naltrexone significantly reduces pain, increases life satisfaction, and improves mood in patients with fibromyalgia.

Sample Transdermal Pain Formulations

Topical combinations can produce anti-inflammatory effects by acting on Peripheral NMDA receptors, blocking cox 1,2 and other various inflammatory mediators.

- **Formula 1**
  - Ketamine 5%, Ketoprofen 10%, Pentoxifylline 5%, Piroxicam 2% in Lipoderm +/- Gabapentin 6%
- **Formula 2**
  - Gabapentin 5%, Ketamine 5%, Ketoprofen 4%
- **Formula 3**
  - Baclofen 10%, Ketoprofen 10%, Lidocaine 10%

Sample Transdermal Pain Formulations

Multiple drugs in one formulation target many mechanisms and could also provide an additive effect to treat conditions such as neuropathic pain.

- **Formula 4**
  - Dextromethorphan 10%, Ketamine 10%, Ketoprofen 10%, Pentoxifylline 10%
- **Formula 5**
  - Amitriptyline 2%, Clonidine 0.2%, Gabapentin 5%, Ketamine 5%, Ketoprofen 5%
- **Formula 6**
  - Amitriptyline 2%, Bupivacaine 2%, Gabapentin 5%, Ketamine 5%, Ketoprofen 5%, Lidocaine 2%

Sample Transdermal Pain Formulations

Deoxy-D-Glucose can be a very effective topical anti-viral medications, and has been seen used with Shingles and Herpetic Sores.

- **Formula 7**
  - Bupivacaine 1%, Clonidine 0.2%, Deoxy-D-Glucose 0.9%, Gabapentin 6%, Ketamine 10% in Lipoderm
- **Formula 8**
  - Amitriptyline 2%, Bupivacaine 3%, Clonidine 0.2%, Gabapentin 6%, Ketamine 10% in Lipoderm

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